EPA CROMERRR MEETING
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INTRODUCTORY STATEMENT

- We appreciate the opportunity to offer comments on the proposed CROMERR Rule and are committed to continuing a relationship with EPA that allows us to better understand one another.
- We recognize the need for regulations and guidance around practices concerning electronic reporting and record-keeping
- While the GLP regulated community is our primary experience and focus, we make up only about 10% of the programs that will be regulated by CROMERRR. Some of our issues are quite similar to those of the environmental community at large, while others may be peculiar to GLP activities. Recognizing there are significant differences in types of data required of GLP-directed programs from the monitoring and data reporting requirements of the other Title 40 programs, we urge you to consider those differences in your decision making process. There may be significant issues for those other Title 40 programs that we will not be providing to you in today's meeting.
- To give you some idea of where regulated entities are coming from when they raise concerns over the cost of upgrading systems and the timing and process for implementation, we'd like to provide a little background. Electronic record-keeping is the norm for GLP-regulated entities and other Title 40 regulated entities alike. The fact that system and business practices have already been established means the coming of CROMERRR will have a significant impact on those regulated entities. For example, one might compare the situation to having built a house using certain materials and blueprints, only to have the building inspector make the occupancy permit contingent upon changing the design of the building and using different materials.
- We'd like to provide some comments now on –
    - different types of records and issues around applying the same criteria to all
    - archiving issues
    - converting to paper records
    - implementation

NOTE: Below are the items we intended to discuss. Items in italics were not addressed due to lack of time (to be addressed later).

I. DATA TYPES

In the GLP world many types of documents, data and reporting formats exist. Although all these documents contribute to the reconstruction of a study, they may be divided into tiers of importance.

Document Types

Original Raw data

Online
- Discrete
  - Electronic Balance
    - Food, Body Wt, organs, chemical/dilutions
  - Bar code ID
    - Animal
    - Chemical
  - Chemical preparation & inventory
  - Dosing/spraying
  - Chemical analysis
  - Field notebook: keyed in directly
    - Issues: temperature, screen visibility, laptop crash, download
  - Activity measurement
  - Animal observations
  - Histopathology
- Continuous
  - Weather
  - Lab Environmental data
    - Temperature
    - Humidity
    - Lights
    - Watering system activity
    - Room entry (animal check)

Hand collected
- Keyboard entry
- Small labs
- Field work

Supporting Documents
- Contaminant analysis for food, water soil
- Correspondence
  - Letters
  - Email
    - Esig
    - User name/password

Data manipulation
- Statistics
- Tables
- Graphs
- Data interpretation
  - Rerun sample

Chromatography integration
Histopathology

Draft Reports
Paper
Electronic
Compound documents
Interim

Standard Operating Procedures
Authored/signed/dated
Retain historical

Training Records
CVs
Training documentation
Technical
Regulations
Education

Logbooks
Equipment calibration
Equipment maintenance

Database Issues
Master Schedule
Archives tracking
Study database
QA audits

Hybrid Documents
Created electronically
Paper signed
Maintained electronically

Created electronically
Signed electronically
Maintained electronically

Compound documents
Assembled electronically
Multiple contributing authors
Complex Toxicology study
Field residue study.

II. ARCHIVING ISSUES

There are a number of archiving issues that have been raised by representatives of regulated companies. We recommend that EPA should carefully consider the FDA-regulated industry experiences with compliance to FDA's 21 CFR Part 11 regulations "Electronic Records: Electronic Signatures" in devising the CROMERRR requirements.

One concern is that the long record retention period that is required by the EPA will result in an unreasonable expectation for long-term electronic record retention under CROMERRR. Because electronic archiving technology is not sufficiently mature, it is expected that regulated entities will continue to archive paper representations of e-records, which will not ultimately result in the reduction of paperwork, as it is hoped. It should be noted that the effective life span of an electronic record system is much shorter than the average record retention period due to rapid changes in software, hardware and storage media technology. It is believed that the CROMERRR does not adequately consider this important issue.

A number of FDA-regulated companies have stated that the FDA vastly underestimated the cost of conformance with 21 CFR Part 11 regulations. We recommend that the concerns and issues regarding 21 CFR 11 should be addressed in the CROMERRR document. A specific example of an issue that continues to cause problems for FDA-regulated companies is the "Guidance for Computerized Systems Used in Clinical Trials" document, which currently provides only two options for providing access to data from discontinued or supplanted systems; by either "maintaining support for the older system, or transcribing data to newer systems."

It is suggested that the EPA adopt the OECD's acceptance of paper printouts as an archive medium as a third alternative. In Section 5 of the OECD Consensus Document, "The Application of the Principles of GLP to Computerized Systems, Environment Monograph 116", OECD recognizes, "raw data in a variety of forms," including instrument printouts. OECD also allows "raw data" to be defined for a computerized system. The definitions of "raw data" are very similar in the OECD and EPA GLPs, but the flexibility found in the OECD interpretation could also give flexibility to CROMERRR, a regulation that is to be applied to a greater variety of programs and situations. Similarly, FDA's "Guidance for Industry: Computerized Systems Used in Clinical Trials" document indicates that a "Certified Copy means a copy of original information that has been verified, as indicated by dated signature, as an exact copy having all of the same attributes and information as the original." It should also be noted that FIFRA GLP §160.190 notes that "Records required by this part may be retained either as original records or as true copies such as photocopies, microfilm, microfiche, or other accurate representations of the original records." On the other hand, 40 CFR 169 has a requirement for retention of original records; applicability to CROMERRR should be clarified.

It is expected that the use of paper printouts of electronic records will require certain controls to assure that they are reliable, complete and accurate. It is recognized that there will be a need for computerized systems to be validated and operated, "…in ways that are compliant with the GLP Principles," including the need for a formal validation plan, validation procedures, documentation of the validation effort and conclusions. In addition, it will be necessary to validate the process that is used to migrate electronic data to newer replacement computer systems, or to certify that paper printouts from the computer system are an accurate and complete copy of the electronic data. There has been much confusion in the FDA-regulated industries regarding this topic, and we recommend that CROMERRR identify what will constitute an acceptable copy of the data that is accurate, reliable and complete. For example, the addition of guidance around acceptable documentation, verification and validation or certification requirements would be beneficial.

In the area of archiving records for the entire record retention period, we suggest that EPA re-evaluate existing record retention times. The current record retention period for FIFRA registration data can be as long as thirty years. Given the rate of technological advances, this

would require numerous costly data migration exercises that would place a significant financial burden on regulated entities. Additionally, we recommend that EPA acknowledge the need for industry and the Agency to work toward acceptable solutions for archiving, without penalizing regulated entities for not having achieved compliance with this requirement.

It is suggested that there should be different record-keeping and archival requirements for different types of systems, instead of developing one set of requirements for all systems. The experience of companies with 21 CFR 11 has demonstrated that the attempts to use the same set of electronic signature and record requirements for all systems results in total company remediation costs and efforts that are unreasonable and not cost-effective. It has been suggested that CROMERRR distinguish between e-records from systems that perform data capture only, vs. those systems that generate and then manipulate, analyze and process data.

Similarly, it might be practical to distinguish between records that represent critical data from records that are used in tracking systems, databases, or for management purposes. CROMERRR should apply the most strict control requirements (audit trails, change control) only for records that represent critical source data, data processing or for data that form the basis for scientific decision-making, and reduce or eliminate these requirements for non-critical, ancillary or management records. The FDA's "Guidance for Industry: Computerized Systems Used in Clinical Trials" document has confused the industry with a statement that, "Any data retrieval software, script, or query logic used for the purpose of manipulating, querying, or extracting data for report generating purposes should be documented and maintained for the life of the report." We feel that the cost of retaining and controlling these "operable" software components is unreasonable, and does not necessarily permit the valid reconstruction of a study because of numerous environmental changes. It is, therefore, recommended that CROMERRR specifically identify the data records that are required to be retained in electronic form, if any, and the necessary access, protection, archival and migration controls for these records only.

It is expected that full technical controls for the paper-based solutions will be necessary in order to reliably replace an electronic record with a paper record. Physical and logical controls will also be necessary for systems that maintain and archive electronic records and documents, such as computerized storage and retrieval archive systems. We recommend the definition of an acceptable data migration strategy that will reliably ensure that data records are protected and are retrievable throughout the record retention period. This strategy should also include requirements for the archival of audit trail information and other meta data. The lack of clarity of the audit trail issues in the 21 CFR Part 11 regulations has caused confusion and unnecessary interpretation, including the planned development of a separate Guidance on audit trails by the FDA.

We further recommend a more practical reconstruction strategy than the one that is provided by the FDA in the "Guidance for "Computerized Systems Used in Clinical Trials." The FDA Guidance notes that the "FDA expects to be able to reconstruct a study" and that "all versions of application software, operating systems, and software development tools involved in processing of data or records should be available as long as data or records associated with these versions are required to be retained." We believe that this method of reconstructing a study is not generally practical because it does not consider changes to hardware, devices and other system components, and it does not consider the impracticality of "rolling-back" and revalidating a complex system to a prior point in time. Although this method is practical for only a relatively limited amount of time, we recommend that, in most cases, the reconstruction of a study will be practical only through a review of archived evidence, and that the study results can only be verified in the current validated environment.

III. CONVERTING E-DATA TO PAPER RECORDS

Introduction: The combination of CROMERRR record keeping requirements with a strict interpretation by EPA of the definition of "raw data" may result in a dramatic step-change in today's business practices for EPA regulated entities. Summarized below are some examples of settings where the proposed CROMERRR requirements for record keeping may not be practical or may result in the adoption of more complicated and costly procedures where there may not be a commensurate benefit in improving data integrity. Also noted below are suggestions for modification to the CROMERRR record keeping requirements that may simplify compliance with GLP principles without compromising the intent of the regulation.

Examples and issues:

Field sites
Field sites often are involved in continuous recording of observation data; i.e., weather conditions or other situations where e-data is captured, but not manipulated in any way. Some of this data gathering equipment is not capable of data storage, or has limited storage capacity, and is typically downloaded to a paper printout and the older electronic data is overwritten with new data. In these cases, the operator typically reviews the printed copy of the data, and signs and dates it to indicate approval.

Environmental monitoring
Environmental monitoring often involves large collections of many data points, where the sum total of the data collected can be represented in a listing of numerical data points. In these cases the data that is captured electronically can be readily verified at the time it is converted, or downloaded to paper. In some cases, the only time that the monitoring data is used is when there is an excursion from what is expected. This type of electronic data is readily represented by a chart or graph.

Electronic balances and pH meters
Laboratories are full of these instruments. The operator often transcribes the data that is generated from a display, in real time. In other cases, the measurement may be transmitted to another instrument, where it is used in an analysis. In these cases, would the raw data be the electronic signal, or would the paper "capture" by the operator or a printer be considered the raw data?

Archiving
The long record retention period that is required by the EPA translates into long-term electronic record retention under CROMERRR. Electronic archiving technology is not developed to the point where companies will rely solely on e-archives, and so it is very likely that regulated entities will continue to archive paper representations of e-records for the foreseeable future. Thus, at this time, CROMERRR may not achieve the reduction of paperwork, as is hoped.

Possible Solutions:

Adopt the OECD interpretation of appropriate use of paper printouts. The OECD Consensus Document "The Application of the Principles of GLP to Computerized Systems, Environment Monograph 116" stresses the need for computerized systems to be validated, and operated "..in ways that are compliant with the GLP Principles," and specifies the need for a validation plan. However, in section 5, OECD recognizes "raw data in a variety of forms," including instrument printouts. OECD also allows "raw data" to be defined for a computerized system. The definitions of "raw data" are very similar in the OECD and EPA GLPs, but the flexibility found in the OECD interpretation could also give flexibility to CROMERRR, a regulation that is to be applied to a great variety of programs and situations.

Distinguish between e-records from systems that perform data capture only, v. those systems that generate and then manipulate, analyze and process data. Allow for downloading to paper for data capture situations. Define adequate verification practices to ensure the integrity of the paper representation of the e-data.

Distinguish between records that represent critical data from records that are used in tracking systems, databases, or for management purposes. Apply strictest control requirements (audit trails, change control) only for records that represent critical data, data processing or for data that form the basis for scientific decision-making, and reduce or eliminate these requirements for non-critical, ancillary or management records. Consider allowing for conversion to paper, and set criteria for verification of the accuracy and completeness of the paper representation of the e-record.

IV. IMPLEMENTATION

CROMERRR,§3.2 Implementation, states that EPA will only accept electronic record-keeping after it has published a notice in the Federal Register announcing that EPA is prepared to recognize electronic records under the named Part or Subpart. This statement causes great concern for the GLP-regulated community, since electronic record-keeping is pervasive in the industry.

Legacy systems will be a significant issue in implementation. The cost of evaluating them against CROMERRR criteria, and replacing or implementing upgrades (because of the numerous systems in question), will be unrealistic for the short-term. Budgets are normally 'bare bones' with little room for the addition of significant non-forecasted expenses. Additionally, technology may not be available for retrofitting systems. Some vendors may not be prepared to implement such upgrades; therefore, procedural controls may be the only short-term solution.

Whatever form the Final Rule takes, we suggest that EPA consider developing and offering compliance guidance as soon as possible. Precedence for this request originates from FDA's recognition and issuance of a Compliance Policy Guide[1] to represent the Agency's thinking on what is required to be fully compliant with 21 CFR Part 11. The Agency set forth several criteria that would be used in assessing whether to pursue regulatory actions for non-compliant entities. These criteria included 1) the nature and extent of the Part 11 deviations, 2) the effect on product quality and data integrity, 3) adequacy and timeliness of planned corrective measures, and 4) compliance history of the establishment, especially with respect to data integrity. By acknowledging that regulated entities would not be compliant immediately, but allowing for them to develop plans that would set forth the steps to be taken in order to achieve compliance, the FDA demonstrated a desire to assist regulated industry in moving toward compliance without penalizing them for their existing state of non-compliance.

[1] Compliance Policy Guide, *Enforcement Policy: 21 CFR Part 11; Electronic Records; Electronic Signatures,* (CPG 7153.17) U.S. FDA Office of Regulatory Affairs, May 13, 1999.

ADDITIONAL ISSUES

- *Can you update us on the status of the OMB comments or actions related to the ICR?*

- *There is some concern about consistency and application of compliance monitoring. Can you give us examples of what sort of training or guidance might be given to the monitoring divisions?*

- We urge EPA to have similar stakeholder meetings with other regulated entities. What will work for GLP-directed entities may not be appropriate for entities that monitor air, water, and other environmental outputs. For many of those other programs, a typical procedure for monitoring activity does not have a finite end when the report is run. Reports tend to be only a point in time look and by the time the report is issued there is already new data available. This puts that part of the industry in a very different situation than the GLP community. The GLP community represents only about 10% of regulated entities that will be impacted by CROMERRR. We urge EPA to have focused discussions with states, large companies, small businesses, and contract facilities that work in those other 90% of the regulated programs.

- *§3.100(a)(2) – It would seem that assuring that a record is maintained without alteration is contradictory to having audit trails for changes to records.*

- *§3.100(a)(9) – We'd like to discuss issues related to migration of complete records, related meta data, and functionality in a new system*.

- *The definition of "electronic record retention system" indicate the system contains "exact electronic copies." Is it the intention for the records requirements to be applied only to systems that contain copies of original records or to all systems?*